ISS small-gain theorem for spatiotemporal delayed dynamics with application to feedback attenuation of pathological brain oscillations

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1 Context and motivations

2 A spatiotemporal rate model for the STN-GPe pacemaker

3 ISS for delayed spatiotemporal dynamics

4 Stabilization of STN-GPe by proportional feedback

5 Conclusion and perspectives

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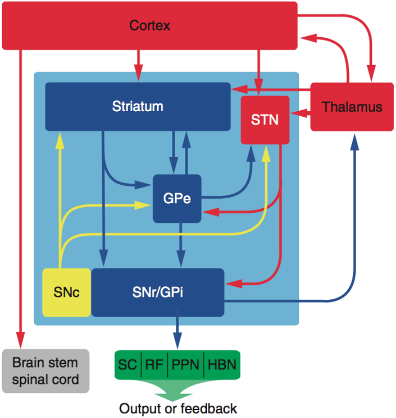
Basal ganglia



[Bolam et al. 2009]

- Basal ganglia (BG) are deep brain nuclei involved in motor, cognitive, associative and mnemonic functions
  - Striatum (Str)
  - External segment of globus pallidus (GPe)
  - Internal segment of globus pallidus (GPi)
  - Subthalamic nucleux (STN)
  - Substantia nigra (SN)
- Interact with cortex, thalamus, brain stem and spinal cord, as well as other structures (superior colliculus (SC), reticular formation (RF), pedunculopontine nucleus (PPN), and lateral habenula (HBN)).

Parkinson's disease and BG activity

- Bursting activity of STN and GPe neurons:

[Ammari et al. 2011]

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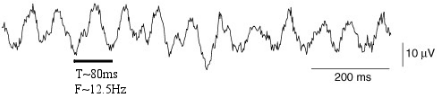
- Local field potential (LFP) in PD STN and GPe show prominent $13 - 30Hz$ (β-band) oscillations:
  - In parkinsonian patients:



[Hammond et al. 2007]

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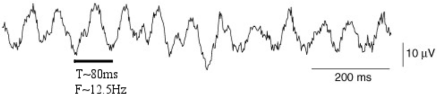

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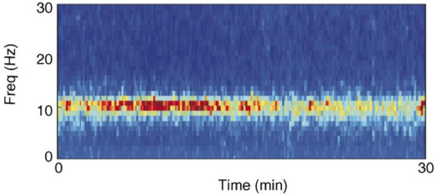
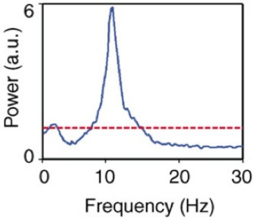
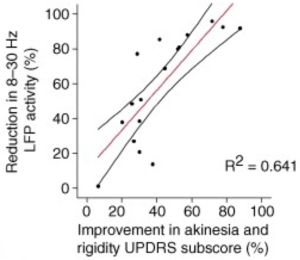
    - In MPTP monkeys:





Parkinson's disease and BG activity

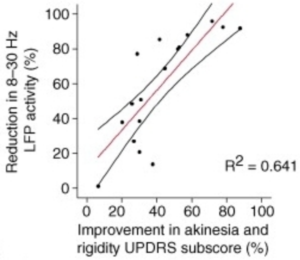
- Reduction of β-band oscillations induces motor symptoms improvement [Hammond et al. 2007, Little et al. 2012]

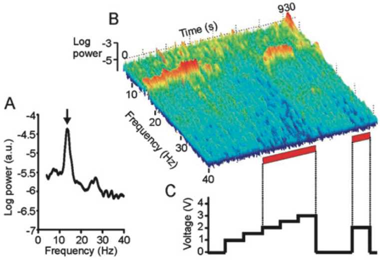


Parkinson's disease and BG activity

- Reduction of β-band oscillations induces motor symptoms improvement [Hammond et al. 2007, Little et al. 2012]

- β-oscillations may decrease during Deep Brain Stimulation [Eusebio et al. 2013]



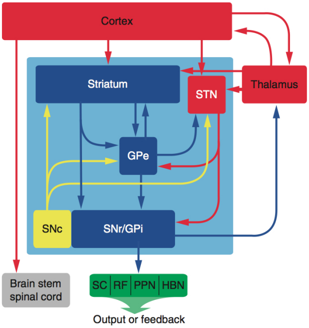


Parkinson's disease and BG activity

Oscillations onset still debated

Parkinsonian symptoms mechanisms are not fully understood either:

- Pacemaker effect of the STN-GPe loop ?
- Striatal endogenous oscillations ?
- Thalamo-cortical relay gating mechanism ?



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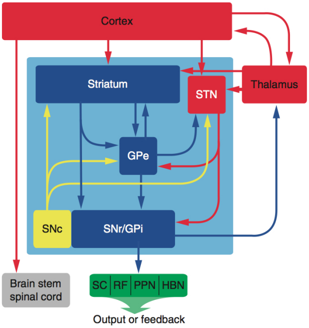

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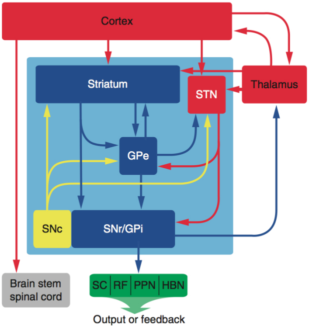

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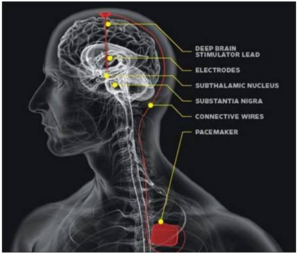
Disrupting pathological oscillations

Technological solutions to steer brain populations dynamics

- Deep Brain Stimulation [Benabid et al. 91]:



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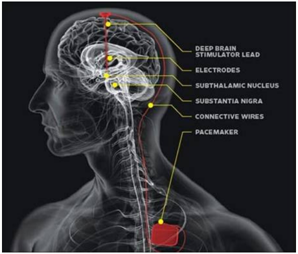
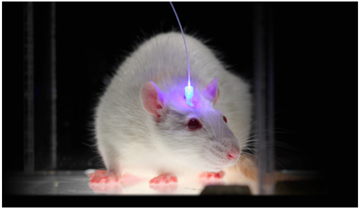


- Optogenetics [Boyden et al. 2005]:



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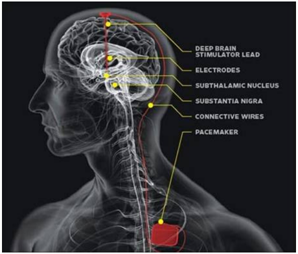

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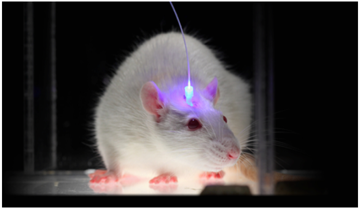

- Acoustic neuromodulation [Eggermont & Tass 2015]
- Sonogenetics [Ibsen et al. 2015]
- Transcranial current stim. [Brittain et al. 2013]
- Transcranial magnetic stim. [Strafella et al. 2004]
- Magnetothermal stim. [Chen et al. 2015]

Some attempts towards closed-loop brain stimulation

Approach	Model	Experimental validation	Analysis tools	Reference
Adaptive & on-demand				
On-demand	-	MPTP primates	-	[Rosin et al. 2011]
On-demand	-	PD patients	-	[Graupe et al. 2010]
On-demand	-	PD patients	-	[Marceglia et al. 2007]
On-demand	-	PD patients	-	[Little et al. 2013]
Adaptive	Conductance-based	-	Artificial neural networks	[Leondopulos 2007]
Adaptive	Conductance-based	-	Simulations	[Santaniello et al. 2011]
Adaptive	Rubin & Terman	-	Optimization	[Feng & Fei 2002]
Delayed & multi-site				
Delayed & multi-site	Conductance-based	MPTP primates in [Tass et al. 2012]	Systems theory in [Pfister & Tass 2010]	[Hauptman et al. 2005]
Delayed & multi-site	Phase dynamics	-	Systems theory	[Omel chenko et al. 2008]
Multi-site	Phase dynamics	-	Simulations	[Lysyansky et al. 2011]
Delayed	Phase dynamics	-	Systems theory	[Rosenblum & Pikovsky 2004]
Proportional, derivative and integral feedback				
Proportional and/or multi-site	-	Culture of cortical neurons	-	[Wagenaar et al. 2005]
Proportional, PID	Phase dynamics	-	Systems theory	[Zheng et al. 2011; Pyragas et al. 2007]
Nonlinear PID	Rulkov model	-	Systems theory	[Tukhlina et al. 2007]
Filtered proportional	Hindmarsh-Rose	-	Simulations	[Luo et al. 2009]
Proportional	Phase dynamics	-	Systems theory	[Franci et al. 2011]
Filtered proportional	Firing rates dynamics	-	Systems theory	[Pasillas-Lépine et al. 2013]
Optimal control				
Optimization	Rubin & Terman	-	Optimization	[Feng & Fei 2002]
Optimal control	Conductance-based	-	Phase response curve	[Danzl et al. 2009]

Modeling neuronal populations

Rate models

Firing rate: instantaneous number of spikes per time unit

- Mesoscopic models
  - Focuses on populations rather than single neurons
  - Allows analytical treatment
  - Well-adapted to experimental constraints
- Relies on Wilson & Cowan model [Wilson & Cowan 1972]
  - Interconnection of an inhibitory and an excitatory populations
  - Too much synaptic strength generates instability
- Simulation analysis: [Gillies et al. 2002, Leblois et al. 2006]
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Modeling neuronal populations

Limitations of existing works

- Spatial heterogeneity needs to be considered:
  - Oscillations onset might be related to local neuronal organization
    [Schwab et al., 2013]
  - Spatial correlation could play a role in PD symptoms
    [Cagnan et al., 2015]
  - Possible exploitation of multi-plot electrodes.
- Techniques needed for analytical treatments of both:
  - Nonlinearities
  - Delays.

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Spatiotemporal model of STN-GPe dynamics

Employed model: **delayed neural fields**

$$\tau_1 \frac{\partial x_1}{\partial t} = -x_1 + S_1\left(\sum_{j=1}^{2}\int_\Omega w_{1j}(r,r')x_j(r',t-d_j(r,r'))dr' + \alpha(r)u(r,t)\right) \tag{1a}$$

$$\tau_2 \frac{\partial x_2}{\partial t} = -x_2 + S_2\left(\sum_{j=1}^{2}\int_\Omega w_{2j}(r,r')x_j(r',t-d_j(r,r'))dr'\right). \tag{1b}$$

- 1: STN population (directly controlled), 2: GPe population (no control)
- $x_i(r,t)$ rate of population i at time t and position $r \in \Omega$
- τ_i: decay rate
- w_{ij}: synaptic weights distributions
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- Spatial extension of [Nevado-Holgado et al. 2010]
  - Stability analysis conducted in [Pasillas-Lépine 2013]
  - Extension to more than two populations [Haidar et al. 2014]

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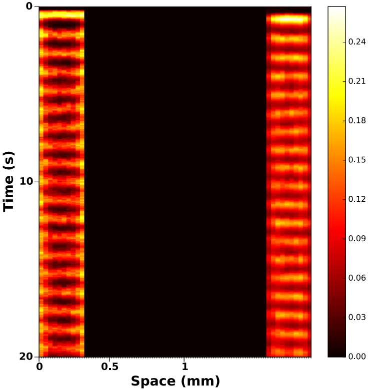
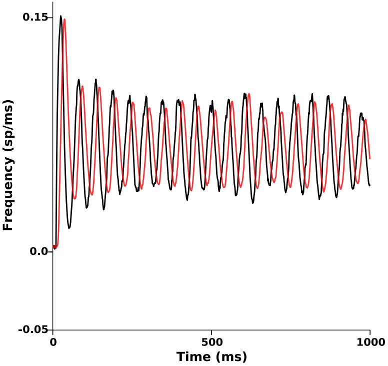
- With parameters inspired from [Nevado-Holgado et al. 2010], generation of **spatiotemporal β-oscillations**:





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ISS for delayed spatiotemporal dynamics

Theoretical framework

Let $\mathcal{F} := L^2(\Omega, \mathbb{R}^n)$ and $\mathcal{C} := C([-\bar{d}; 0], \mathcal{F})$.

Consider generic delayed spatiotemporal dynamics:

$$\dot{x}(t) = f(x_t, p(t)), \tag{2}$$

where

- $f : \mathcal{C} \times \mathcal{U} \to \mathcal{F}$
- $x(t) \in \mathcal{F}^n$ is the state: at each time instant t, it is a *function* of the space variable
- For each $\theta \in [-\bar{d}; 0]$, $x_t(\theta) := x(t + \theta)$.
- $p \in \mathcal{U}$ is an exogenous input.

Associated norms [Faye & Faugeras 2010]:

- $\|x\|_{\mathcal{F}} := \sqrt{\int_\Omega |x(s)|^2 ds}$ for all $x \in \mathcal{F}$
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Definition

Definition: Input-to-state stability

The system (2) is *ISS* if there exist $\beta \in \mathcal{KL}$ and $\nu \in \mathcal{K}_\infty$ such that, for any $x_0 \in \mathcal{C}$ and any input $p \in \mathcal{U}$,

$$\|x(t)\|_{\mathcal{F}} \leq \beta(\|x_0\|_{\mathcal{C}}, t) + \nu\left(\sup_{\tau \geq 0} \|p(\tau)\|_{\mathcal{F}}\right), \quad \forall t \in \mathbb{R}_{\geq 0}.$$

- Delayed spatiotemporal extension of ISS [Sontag]
- Spatiotemporal extension of [Pepe & Jiang 2006]
- Global asymptotic stability in the absence of input
- Steady-state error "proportional" to input magnitude.

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Lyapunov-Krasovskii sufficient condition

Theorem: Lyapunov-Krasovskii function for ISS

Let $\underline{\alpha}, \overline{\alpha}, \alpha, \gamma \in \mathcal{K}_\infty$ and $V \in C(\mathcal{C}, \mathbb{R}_{\geq 0})$, and assume that, given any $x_0 \in \mathcal{C}$ and any $p \in \mathcal{U}$, the system (2) admits a unique solution defined over $[-\bar{d}; +\infty)$ and satisfying

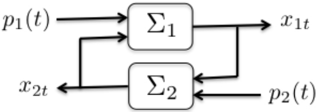
$$\underline{\alpha}(\|x(t)\|_{\mathcal{F}}) \leq V(x_t) \leq \overline{\alpha}(\|x_t\|_{\mathcal{C}}) \tag{3}$$

$$\|x_t\|_{\mathcal{C}} \geq \gamma(\|p(t)\|_{\mathcal{F}}) \quad \Rightarrow \quad \dot{V}^{(2)} \leq -\alpha(V(x_t)). \tag{4}$$

Then the system (2) is ISS.

ISS for delayed spatiotemporal dynamics

Small-gain theorem



$$\dot{x}_1(t) = f_1(x_{1t}, x_{2t}, p_1(t)) \tag{5a}$$

$$\dot{x}_2(t) = f_2(x_{2t}, x_{1t}, p_2(t)) \tag{5b}$$

Theorem: ISS small gain (along the lines of [Pepe & Jiang 2006])

Let $\underline{\alpha}_i, \overline{\alpha}_i, \alpha_i, \gamma_i, \chi_i \in \mathcal{K}_\infty$ and $V_i : \mathcal{C} \to \mathbb{R}_{\geq 0}$, and assume that, given any $x_{i0} \in \mathcal{C}$ and any $p_i \in \mathcal{U}$,

$$\underline{\alpha}_i(\|x_i(t)\|_{\mathcal{F}}) \leq V_i(x_{it}) \leq \overline{\alpha}_i(\|x_{it}\|_{\mathcal{C}}) \tag{6}$$

$$V_1 \geq \max\{\chi_1(V_2), \gamma_1(\|p_1(t)\|_{\mathcal{F}})\} \quad \Rightarrow \quad \dot{V}_1^{(5a)} \leq -\alpha_1(V_1) \tag{7}$$

$$V_2 \geq \max\{\chi_2(V_1), \gamma_2(\|p_2(t)\|_{\mathcal{F}})\} \quad \Rightarrow \quad \dot{V}_2^{(5b)} \leq -\alpha_2(V_2). \tag{8}$$

Then, under the small-gain condition

$$\chi_1 \circ \chi_2(s) < s, \quad \forall s > 0, \tag{9}$$

the feedback interconnection (5) is ISS.

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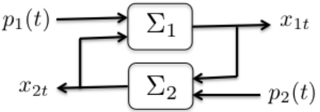

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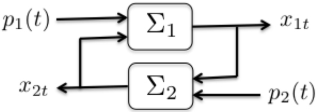

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1 Context and motivations

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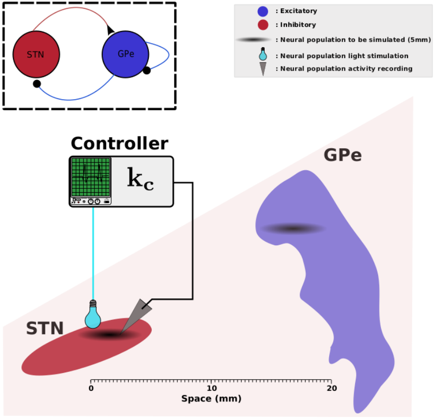
4 Stabilization of STN-GPe by proportional feedback

5 Conclusion and perspectives

Proportional feedback on STN



Control input: $u(r,t) = -kx_1(r,t)$:

- Similar control in an averaged model: [Pasillas-Lépine et al. 2013]
- No measurement or control on GPe required.

Main result: stabilizability by proportional feedback

$$\tau_1 \frac{\partial x_1}{\partial t} = -x_1 + S_1 \left(\sum_{j=1}^{2} \int_\Omega w_{1j}(r,r') x_j(r', t - d_j(r,r')) dr' + \alpha(r) u(r,t) \right)$$

$$\tau_2 \frac{\partial x_2}{\partial t} = -x_2 + S_2 \left(\sum_{j=1}^{2} \int_\Omega w_{2j}(r,r') x_j(r', t - d_j(r,r')) dr' \right).$$

Theorem: ISS stabilization with partial measurement/actuation

Assume that S_i are nondecreasing and ℓ_i-Lipschitz. If

$$\int_\Omega \int_\Omega w_{22}(r,r')^2 dr' dr < \frac{1}{\ell_2} \tag{10}$$

then there exists $k^* > 0$ such that, for any $k \geq k^*$, the proportional feedback $u(r,t) = -kx_1(r,t)$ makes the coupled neural fields ISS.

- (10) imposes that oscillations are not endogenous to GPe (weak internal coupling: in line with neurophysiology literature)
- No precise knowledge of parameters required
- Easy tuning.

Main result: stabilizability by proportional feedback

$$\tau_1 \frac{\partial x_1}{\partial t} = -x_1 + S_1 \left(\sum_{j=1}^{2} \int_\Omega w_{1j}(r, r') x_j(r', t - d_j(r, r')) dr' + \alpha(r) u(r, t) \right)$$

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Sketch of proof

1. Show that GPe is ISS under condition (10) with

$$V_2(x_{2t}) := \frac{\tau_2}{2}\int_\Omega x_2(r,t)^2 dr + \int_\Omega \beta(r)\int_\Omega\int_{-d_2(r,r')}^{0} e^{c\theta} x_2(r',t+\theta)^2 d\theta dr' dr.$$

2. Show that, for k large enough, STN is ISS with arbitrarily small ISS-gain

$$V_1(x_{1t}) := \frac{\tau_1}{2}\int_\Omega x_1(r,t)^2 dr + \frac{\tau_1}{2\#\Omega}\int_\Omega\int_\Omega\int_{-d_1(r,r')}^{0} e^{\theta} x_1(r',t+\theta)^2 d\theta dr' dr.$$

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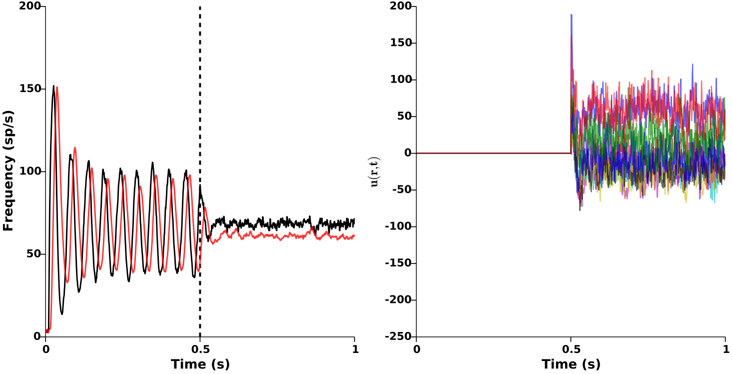
Simulations



Efficient attenuation of pathological oscillations
using proportional feedback on STN.

Consequences of ISS

Robustness to feedback delays

Estimation of STN activity requires acquisition and computation time: $u(r,t) = -kx_1(r, t - d_c(r))$.

Proposition: Robustness to feedback delays

Under the same assumptions, consider any $k \geq k^*$ and assume that S_1 is bounded. Then there exists a function $\nu \in \mathcal{K}_\infty$ such that

$$\limsup_{t\to\infty} \|x(t)\|_{\mathcal{F}} \leq \nu\left(\sup_{r\in\Omega} d_c(r)\right).$$

- Magnitude of remaining oscillations "proportional" to acquisition/processing delays
- Requires a bounded activation function on the STN.

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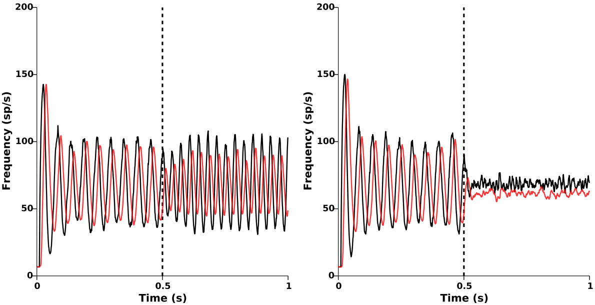

STN and GPe mean activity with acquisition/processing delays of 10ms (left) and 5ms (right).

Consequences of ISS

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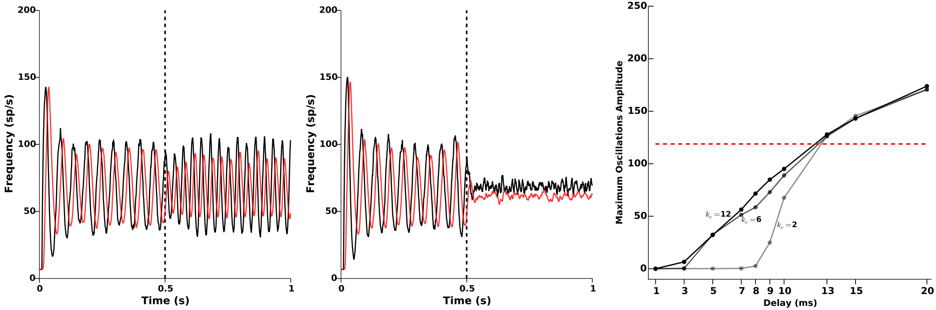

STN and GPe mean activity with acquisition/processing delays of 10ms (left) and 5ms (right).

STN oscillations magnitude as a function of acquisition/processing delays.

Consequences of ISS

Homogeneous control signal

In practice (e.g. optogenetics), the whole STN receives the same stimulation signal: $u(t) = -\int_\Omega \alpha'(r)x_1(r,t)dr$.

Measure of heterogeneity: $\mathcal{H}(q) := \sqrt{\int_\Omega \int_\Omega (q(r) - q(r'))^2 dr' dr}$.

Proposition: Practical stabilization by homogeneous feedback

Under the same assumptions, consider any $k \geq k^*$. Assume that the activation functions S_i are bounded and that the delay distributions d_i are homogeneous ($d_i(r,r') = d_i^*$). Then there exist $\nu_1, \nu_2 \in \mathcal{K}_\infty$ such that

$$\limsup_{t\to\infty} \|x(t)\|_{\mathcal{F}} \leq \nu_1 \left(\mathcal{H}(w_{11}) + \mathcal{H}(w_{12})\right) + \nu_2 \left(\mathcal{H}(\alpha)\right).$$

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Homogeneous control signal: sketch of proof

1. Considering $W(x_1(t)) = \mathcal{H}_1(x_1(t))^2$, show that

$$\mathcal{H}(x_1(t)) \leq \mathcal{H}(x_1(t_0))e^{-(t-t_0)/\tau_1^*} + c\left(\mathcal{H}(w_{11}) + \mathcal{H}(w_{12}) + \mathcal{H}(\alpha)\right).$$

2. Evaluate the difference between the nominal control and the uniform one:

$$\int_\Omega \left(\int_\Omega \alpha'(r')x_1(t,r')dr' - x_1(t,r) \right)^2 dr \leq c\mathcal{H}(x_1(t))^2.$$

3. Exploit the "asymptotic gain property" induced by ISS.

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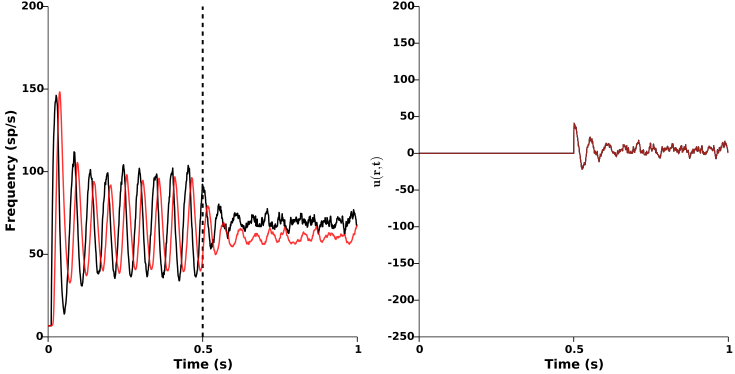

Efficient attenuation of pathological oscillations using homogeneous feedback on STN.

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Conclusion and perspectives

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  - A framework for ISS of delayed spatiotemporal dynamics:
  - A spatiotemporal model of STN-GPe generating β-oscillations
  - A condition for ISS-stabilizability by proportional feedback on STN
- What remains to be done:
  - Delay-dependent conditions for stabilizability
  - Increased robustness to acquisition/processing delays: in the spirit of [Pasillas-Lépine et al. 2013]
  - More precise modeling of actuator dynamics
  - Strategies that preserve non-pathological oscillations
  - Indirect (cortical) stimulation
  - Precise model, identified on a unique animal in health and disease (ANR project SynchNeuro).

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Related publications

- G. Is. Detorakis, A. Chaillet, S. Palfi, S. Senova. Closed-loop stimulation of a delayed neural fields model of parkinsonian STN-GPe network: a theoretical and computational study. *Frontiers in Neuroscience*, 2015.
- I. Haidar, W. Pasillas-Lépine, E. Panteley, A. Chaillet, S. Palfi and S. Senova. Analysis of delay-induced basal ganglia oscillations: the role of external excitatory nuclei. *International Journal of Control*, 2014.
- R. Carron, A. Chaillet, A. Filipchuk, W. Pasillas-Lépine, and C. Hammond. Closing the loop of Deep Brain Stimulation. *Frontiers in Systems Neuroscience*, 7 (112): 1-18, Dec. 2013.
- A. Chaillet, A.Yu. Pogromsky, and B.S. Rüffer. A Razumikhin approach for the incremental stability of delayed nonlinear systems. *Proc. IEEE Conf. on Decision and Control*, Florence, Italy, Dec. 2013.
- W. Pasillas-Lépine, H. Haidar, A. Chaillet, and E. Panteley. Closed-loop Deep Brain Stimulation based on firing-rate regulation, *Proc. 6th IEEE EMBS Conf. on Neural Engineering*, San Diego, USA, 2013.